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Blood Gas and Acid-Base Status of Conscious Pigs Subjected to Fixed-Volume Hemorrhage and Resuscitated With Hypertonic Saline Dextran

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Conscious, chronically instrumented pigs were subjected to a progressive, fixed-volume hemorrhage (37.5 ml/kg over 1 h) and subsequent resuscitation with 7.5% hemorrhage (37.5 ml/kg over 1 h) and subsequent resuscitation with 7.5% NaCl/6% Dextran 70 (4 ml/kg). Hemorrhage led to increases in arterial PO_2 , HbO_2 , plasma lactate, base deficit, and mixed venous PCO_2 . It led to decreases in arterial PCO_2 , plasma bicarbonate, and buffer base, as well as mixed venous PO_2 , HbO_2 , and pH. These effects were attributable to reduced O_2 delivery, lactic acidemia, hyperventilation, and hemodilution. Resuscitation with hypertonic saline/dextran produced a transient increase in arterial PCO_2 and base deficit and a transient decrease in pH, effects that were attributable to a transfer of venous blood attributes to the arterial circulation. Resuscitation also produced an immediate decrease in arterial buffer base, an effect attributable to hemodilution. Subsequently, over 4 h, most cardiopulmonary and metabolic variables gradually reverted toward control levels, thereby ameliorating the deleterious blood gas and acid-base disturbances produced by severe hemorrhage.

Key words: swine, blood loss, lactic acidemia, arterial, mixed-venous, base deficit, buffer base, hypertonic saline/dextran

INTRODUCTION

In a recent study of conscious pigs subjected to a progressive, normally lethal, fixed-volume hemorrhage, we observed an increase in total body O_2 consumption, an

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effect that was associated with an increase in skeletal muscle activity [1]. This behavioral compensation presumably enhanced venous return and cardiac output during hypovolemia, but it did not sufficiently enhance arterial O_2 delivery to offset the O_2 demand of body tissues. As a consequence, body energy needs during the course of hemorrhage became increasingly dependent upon anaerobic glycolysis, which in turn caused an escalation of lactic acid production. Additional compensations elicited by hemorrhagic hypotension included hyperventilation to eliminate CO_2 generated by hypermetabolism and transcapillary refill to replenish blood volume. Subsequent to hemorrhage, these pigs were resuscitated with 7.5% NaCl/6% Dextran 70, a treatment that reduced tissue O_2 demand and produced a significant improvement in survival [2].

The foregoing metabolic, ventilatory, and vascular fluid alterations led to numerous changes in blood gas and acid-base status, the subject of the present report. In evaluating these changes, we were specifically concerned with the following questions: Do the compensatory responses normally mobilized by conscious pigs effectively ameliorate the adverse blood gas and acid-base effects of severe blood loss? To what extent during hemorrhage are the various components of the blood buffer system altered by lactacidemia and transcapillary refill? Finally, does resuscitation with hypertonic saline/dextran produce improvements in blood gas and acid-base status that contribute to survival of hypovolemic animals?

MATERIALS AND METHODS

Three groups of immature Yorkshire pigs were used in the studies reported here. One group ($n = 6$) was subjected to severe hemorrhage and resuscitated with 7.5% NaCl/6% Dextran 70; a second, control group ($n = 8$) was subjected to the same hemorrhage regimen but resuscitated with 0.9% NaCl; and a third group ($n = 8$) was subjected to neither hemorrhage nor resuscitation and served as controls for the effects of physical restraint in another simultaneously conducted study [3] as well as the study reported here. As described elsewhere [1,2], the pigs were chronically instrumented with carotid and pulmonary artery catheters. At the same time, a splenectomy was performed, and a sideport catheter [4] was chronically implanted in the aorta distal to the kidneys. Over a 3 day period before surgery and recommencing 2 days thereafter, the pigs were trained 60 min daily to accept a respiratory mask and physical restraint in a Pavlov sling.

On the day of study, each pig was brought into the laboratory and placed in the sling with the mask secured over the snout; the mask was used to record ventilatory and metabolic variables as reported elsewhere [1]. The carotid and pulmonary artery catheters were connected by pressure-injection lines to 3-way stopcocks and pressure transducers for measurements of hemodynamic and O_2 delivery variables [1,2], and for sample removal to determine blood gas and acid-base status. The sideport catheter also was connected to a 3-way stopcock to allow blood removal during the hemorrhage phase of the study. Stagnant blood and heparinized saline were cleared from all 3 catheters and they were refilled with fresh heparinized saline (100 units/ml). The animal was allowed to remain quietly in the sling until minimal O_2 consumption values were achieved and maintained for at least 10 min. This rest interval ranged from 30 to 60 minutes. Control measurements were taken in triplicate at 10-min intervals, and hemorrhage was initiated immediately thereafter. Blood was

progressively removed from the animal on an exponential scale over a 60 min period to achieve a total hemorrhage volume of 37.5 ml/kg. Blood samples were taken from the carotid and pulmonary arteries at 9, 19, 31.5, 44, and 60 min (i.e., after successive 7.5 ml/kg increments of blood loss) for measurements of blood gas and acid-base status. Immediately after hemorrhage, the pig was given a 4 ml/kg bolus injection of 7.5% NaCl/6% Dextran 70 into the pulmonary artery, and additional blood samples were taken at 5, 15, 30, 60, 180, and 240 min of the subsequent recovery period. Sample volumes removed during the control and hemorrhage phases of the study were included in the hemorrhage volume.

Blood gas and acid-base measurements were made at 38.5°C, the normal core temperature of domestic pigs [5], immediately after sample removal using an Instrumentation Laboratory Model 1303 blood gas analyzer and Model 282 Cooximeter (Instrumentation Laboratory Inc., Lexington, MA). Both instruments were calibrated and maintained according to the manufacturer specifications. Plasma lactate concentration was measured enzymatically using a GEMSAEC autoanalyzer (Electronucleonics, Inc., Fairfield, NJ) and Sigmasystem test kits (Sigma Chemical Co., St Louis), and plasma protein concentration was determined colorimetrically using a Bio-Rad protein assay (Bio-Rad Laboratories, Richmond, CA). Plasma protein anion concentration was calculated by the Van Slyke equation [6]:

$$\text{Protein anion (mEq/L)} = 0.104(\text{g protein/L})(\text{pH}_a - 5.08)$$

Buffer base concentration and changes in base deficit were estimated by nomograms specific for pig blood [7]. These nomogram values were corrected for losses of plasma protein anion during and subsequent to hemorrhage.

Single-factor (time) and two-factor (treatment, time) analyses of variance were used as appropriate for within- and between-group comparisons. The single factor evaluation of pigs resuscitated with 7.5% NaCl/6% dextran was first applied to the hemorrhage period and then to the first hour of recovery, i.e., before any animals had died. In addition, mean \pm SEM values were calculated for each time point during the control, hemorrhage, and recovery periods. At 1 hour and thereafter during the recovery period, two mean values were calculated for the time point that preceded death of an animal: one mean included and the other excluded the nonsurviving animal. This double calculation was directed at minimizing data distortion that might result from changes in interanimal variance associated with a reduction in group size. Representative SEM values are indicated in the figures that follow.

RESULTS

Prolonged physical restraint in a Pavlov sling had no significant effect on the blood gas or acid-base status of control pigs that were neither hemorrhaged nor resuscitated. The values recorded in these animals, furthermore, were not significantly different from those recorded at zero time (before hemorrhage) in the other two groups of pigs.

Control pigs subjected to hemorrhage and resuscitated with 0.9% NaCl showed blood gas and acid-base responses during hemorrhage that were nearly identical with those recorded in pigs resuscitated with 7.5% NaCl/6% dextran. Resuscitation with 0.9% NaCl was ineffective, and all of these animals died shortly after the procedure

was initiated [3]. Nonsurvival of these animals precluded statistical evaluation of their resuscitation data.

Of the six pigs receiving 7.5% NaCl/6% Dextran 70, four survived beyond the 240 min experimental period. Two died, one at 70 min and the other at 190 min after resuscitation. Death was preceded by progressively more pronounced hypoventilation, lacticacidemia, and hypometabolism, and ultimately cardiac arrest.

A progressive and significant increase in arterial PO_2 , from 85 ± 1.4 to 102 ± 3.0 torr, was observed over the course of the hemorrhage episode (Fig. 1A). Mixed venous PO_2 , in contrast, decreased significantly during hemorrhage, from 41 ± 1.3 to 17 ± 2.1 torr (Fig. 1B). Opposite effects also were seen following resuscitation with hypertonic saline/dextran. At the 5-min point following treatment, arterial PO_2 was reduced by 4.5 torr, while mixed venous PO_2 was increased by 16 torr. These effects of hypertonic saline/dextran, though statistically significant overall, were not sustained on the venous side of the circulation during the remainder of the recovery period. Rather, they regressed to levels intermediate to those recorded before and immediately after hemorrhage. Arterial PO_2 gradually returned toward control levels as recovery progressed.

The effects of hemorrhage and hypertonic saline/dextran resuscitation on arterial (Fig. 1C) and mixed venous (Fig. 1D) oxygen saturation were consistent with expectations. The values rose and fell significantly in accordance with changes in PO_2 . Again, treatment had a more pronounced effect on the venous side, the HbO_2 values rising from $12.6 \pm 2.47\%$ at the end of hemorrhage to $30.5 \pm 5.27\%$ at 5 min into the recovery period. Impending death of animals during the recovery period, one at 130 and the other at 250 min into the overall experiment, had a tendency to distort mean and SEM values for both PO_2 and HbO_2 . At the 120 min point, for example, the pig that subsequently died had an arterial PO_2 value that was 11 torr higher than the mean for the remainder of the group.

Hemorrhage caused a significant, progressive decrease in arterial PCO_2 , from 42 ± 1.0 to 28 ± 2.9 torr, and a progressive increase in mixed venous PCO_2 , from 49 ± 0.9 to 58 ± 2.5 torr (Fig. 2A,B). The bolus of 7.5% NaCl/6% dextran produced an abrupt and significant reversal of both changes, arterial PCO_2 rising to 36 ± 1.7 torr and mixed venous PCO_2 decreasing to 51 ± 1.8 torr at 5 min into the recovery period. Subsequent arterial values rose slowly toward, but did not reach, prehemorrhage control levels. Subsequent venous values were actually lower than control levels.

Despite the marked reduction in arterial PCO_2 during hemorrhage, arterial pH was not significantly altered (Fig. 2C). Mixed venous pH, however, showed a significant, progressive decline from 7.39 ± 0.011 to 7.19 ± 0.022 (Fig. 2D). Resuscitation with hypertonic saline/dextran had an immediate effect on arterial but not on venous pH. At 5 min into the recovery period, arterial pH was reduced from a post-hemorrhage level of 7.41 ± 0.044 to 7.25 ± 0.021 , while venous pH remained essentially unchanged. Thereafter, both arterial and venous pH values reverted toward control levels. Impending death was associated with a tendency for lowered arterial and venous PCO_2 values. This tendency was particularly evident in arterial blood measurements made at 240 min into the overall experimental period (Fig. 2A); the nonsurviving animal had a PCO_2 value that was 11 torr below the mean for the surviving animals. Progressive hypoventilation during the agonal phase reversed this tendency.

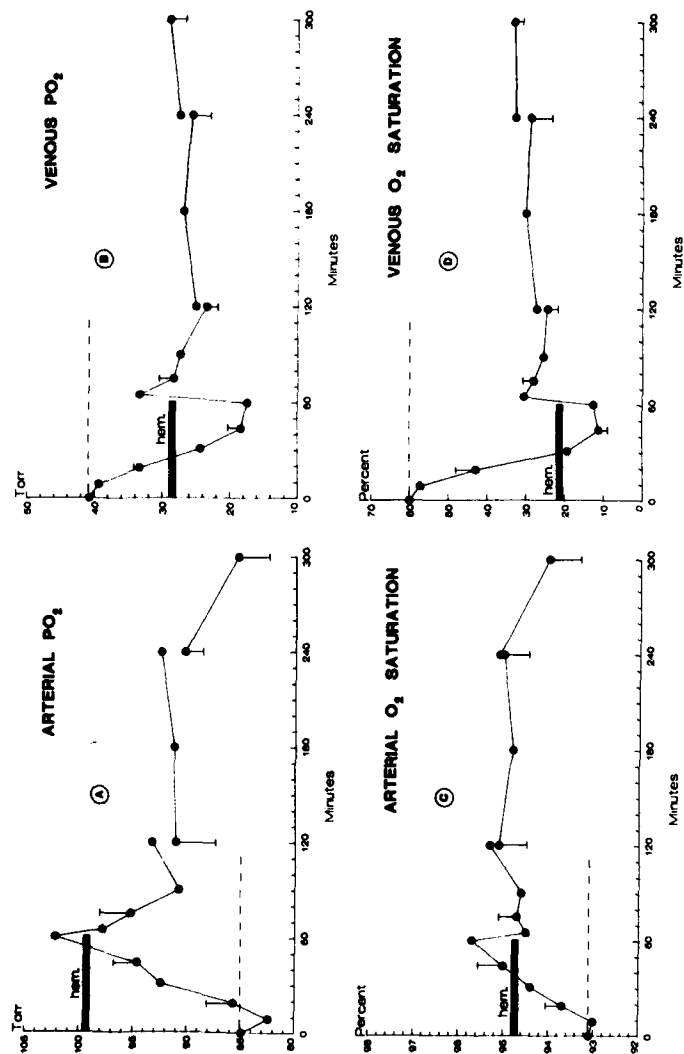


Fig. 1. Effects of progressive fixed-volume hemorrhage (37.5 ml/kg) followed by resuscitation with 7.5% NaCl/6% dextran on arterial and mixed venous blood oxygenation. Resuscitation (4 ml/kg) was provided immediately (over 1 min) after hemorrhage. Breaks in the plots indicate time points at which mean and S.E.M. values were calculated to include as well as exclude an animal that died shortly thereafter. Solid bar depicts hemorrhage interval, dashed line control level for each variable.

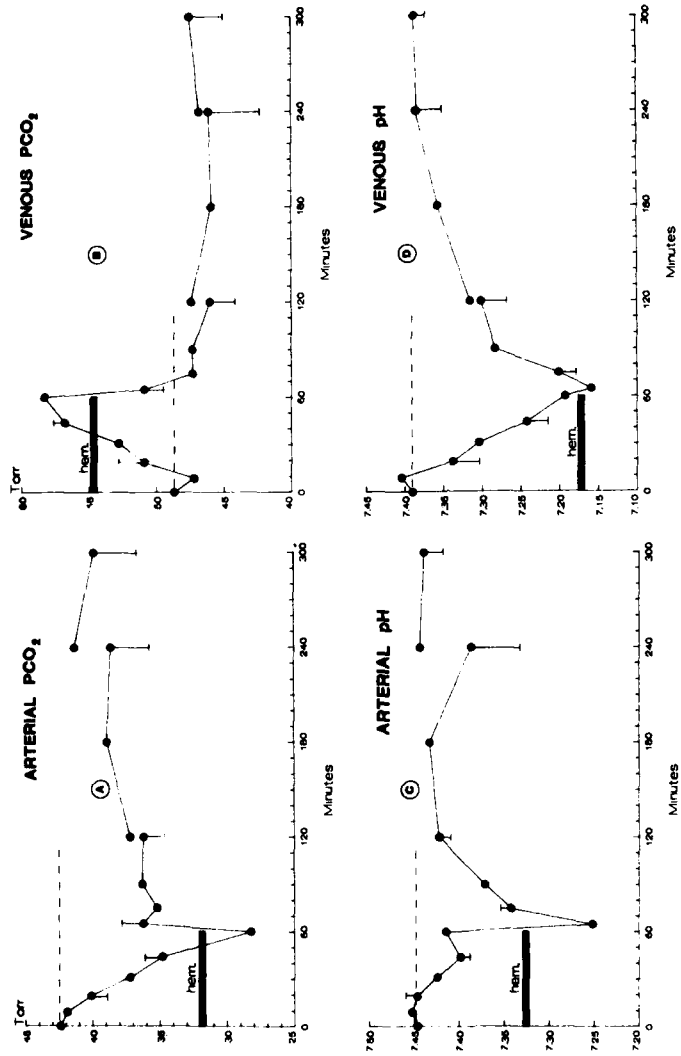


Fig. 2. Effects of progressive-fixed volume hemorrhage followed by resuscitation with hypertonic saline/dextran on the pH and PCO₂ of arterial and mixed venous blood. See Figure 1 for details.

A significant, progressive reduction in the concentration of bicarbonate in arterial plasma was recorded during hemorrhage (Fig. 3A), an effect that was associated with concomitant and nearly equivalent increments in plasma lactate concentration (Fig. 3B). Accordingly, bicarbonate was reduced from 29.5 ± 0.73 to 17.5 ± 0.94 mEq/L, a change of 12 mEq/L, while lactate increased from 0.6 ± 0.04 to 13.6 ± 1.03 mEq/L, a change of 13 mEq/L. The bolus of 7.5% NaCl/6% dextran had little immediate effect on plasma bicarbonate or lactate concentrations, but over the course of recovery both variables gradually and significantly reverted toward prehemorrhage control levels.

Arterial base deficit (Fig. 3C) increased significantly, by 14.4 ± 0.67 mEq/L, over the course of hemorrhage, a change that was about 2.4 mEq/L greater than the decrease in plasma bicarbonate concentration. Treatment with hypertonic saline/dextran led to an immediate further increase in arterial base deficit (of 4.6 ± 0.58

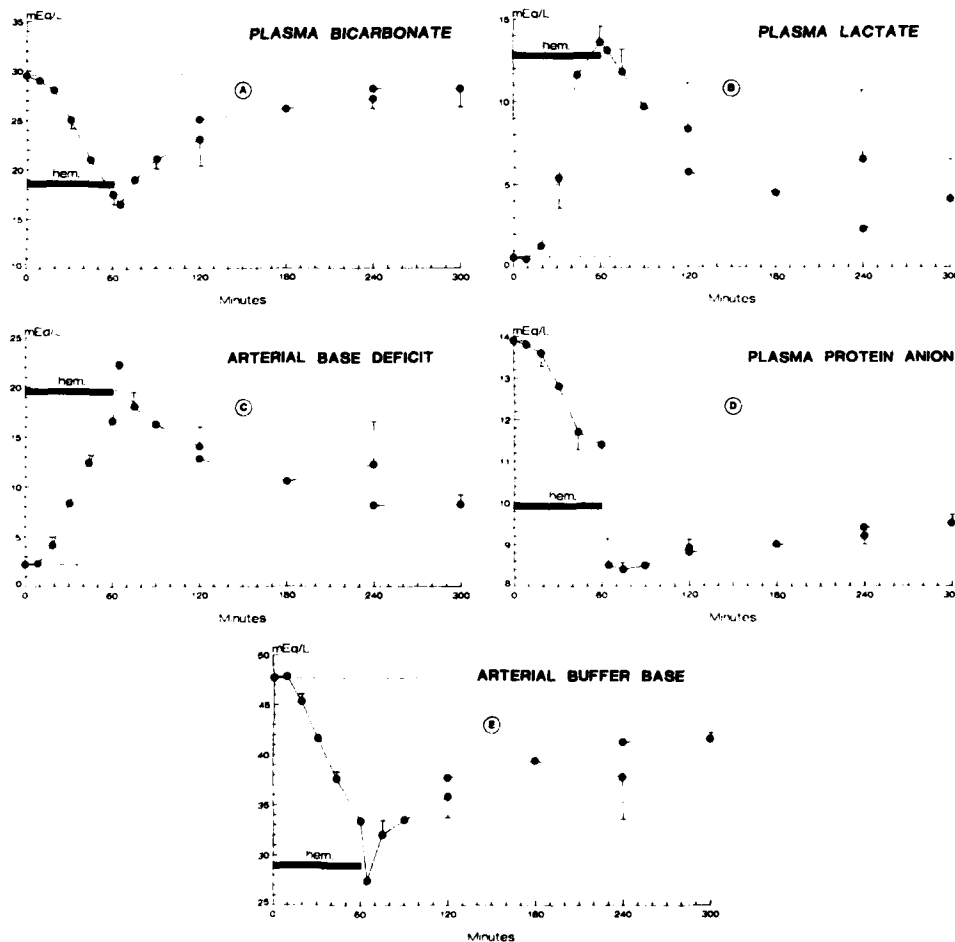


Fig. 3. Effects of progressive fixed-volume hemorrhage followed by resuscitation with hypertonic saline/dextran on plasma bicarbonate, lactate and protein anion concentrations and on base deficit and buffer base concentrations of arterial blood. See Figure 1 for details.

mEq/L), but thereafter the values gradually returned toward control levels. Again, nonsurviving animals tended to distort mean and SEM values during recovery.

The concentration of plasma protein anion decreased progressively and significantly during hemorrhage, from 13.9 ± 0.33 to 11.4 ± 0.38 mEq/L (Fig. 3D). Following treatment with hypertonic saline/dextran, a sharp additional decrease (to 9.7 ± 0.19 mEq/L) was recorded at 5 min into the recovery period. Subsequently, the values rose gradually but significantly as the recovery period was extended to 4 h.

Arterial buffer base also showed a significant progressive decrease during hemorrhage, from 47.7 ± 0.64 to 33.4 ± 0.84 mEq/L (Fig. 3E). At the 5-min point following treatment with 7.5% NaCl/6% dextran, a further decrease to 27.1 ± 1.42 mEq/L was recorded. At this time period, therefore, the buffering capacity of the arterial blood was reduced to approximately 57% of the control level. Over the remainder of the recovery period, buffer base values gradually recovered, reaching about 86% of the control level at the 4-hr point.

DISCUSSION

Hemorrhage Effects

As reported previously for these same pigs [1], hemorrhage caused a modest rise in O_2 consumption, a reduction in cardiac output and arterial O_2 delivery, marked metabolic acidosis, hemodilution, and hyperventilation, effects that increased in magnitude as hemorrhage progressed. In large measure, these functional changes were responsible for the blood gas and acid-base changes recorded here. Hyperventilation, for example, caused the increase in arterial oxygen tension and saturation seen in the present study and other studies of hemorrhagic hypotension in conscious pigs [8,9]. Increased tissue O_2 extraction from perfusing blood was responsible for the decrements in mixed venous PO_2 and O_2 saturation, and lactacidemia with a resultant breakdown of bicarbonate was responsible for the increase in mixed venous PCO_2 and the decreases in plasma bicarbonate and mixed venous pH. The unchanged arterial pH recorded here, and by others in conscious pigs [10–13], attests to the compensatory effectiveness of hyperventilatory CO_2 removal in ameliorating the adverse effects of lactacidemia. Anesthetized pigs, in contrast, oftentimes show a significant decrease in arterial pH during hemorrhage. In animals that are allowed to breathe spontaneously [14–16], the decrease appears to be attributable to ventilatory suppression by the anesthetic. In anesthetized animals that are mechanically ventilated to maintain a constant arterial PCO_2 [17–19], the decrease in arterial pH appears to be attributable to insufficient CO_2 removal from mixed venous blood. Both of these circumstances lead to a reduction in ratio of bicarbonate to CO_2 , hence a decrease in pH. A more relevant approach, at least in terms of simulating the characteristics of conscious animals, would be to regulate mechanical ventilation to maintain a constant arterial pH.

Bicarbonate loss was a major contributor to the reduced blood buffer base and the elevated base deficit concentrations associated with severe hemorrhage. Perhaps not so readily apparent were the buffer base changes attributable to decrements in hemoglobin and plasma protein concentrations, a subject that has not been examined in previous studies of porcine hemorrhage. In the present investigation, the contribution of hemoglobin to blood buffering capacity was automatically taken into account when porcine alignment nomograms were used to estimate buffer base and

base deficit concentrations [7]; these nomograms incorporated corrections for changes in hemoglobin concentration. Under the conditions of the present study, hemoglobin loss during hemorrhage was responsible for only a small portion of the total decrease in blood buffering capacity, about 1 mEq/L. These nomograms, however, like those for human blood, did not provide corrections for changes in plasma protein concentration. Their construction was based on an average population value for protein concentration [7], a value that was appropriate for our control measurements but was not appropriate for measurements made during hemorrhage.

During hemorrhage, transcapillary refill [1] leads to a progressive decrease in the concentration of plasma protein anion (2.5 mEq/L in the present study), and corrections have to be made for the resultant decrements in buffer base (see "Materials and Methods"). Insofar as can be determined, similar corrections were not made in other studies of the buffer base or base excess changes associated with hemorrhage, hence the decrements in buffer concentration were underestimated. When pigs are used as the animal model, additional inaccuracies arise when acid-base measurements are based on the underlying characteristics of human blood; the buffer characteristics of porcine blood are distinctly different from those of human blood [7].

Resuscitation Effects

Administration of hypertonic saline/dextran following hemorrhage produced both acute and chronic alterations in blood gas and acid-base status. Acutely, hypertonic saline/dextran led to a marked rise in mixed venous PO_2 and a modest decrease in arterial PO_2 . It also produced an acute rise in arterial PCO_2 which in turn caused arterial pH to decrease sharply. The PCO_2 of mixed venous blood, on the other hand, was reduced almost to control levels. In terms of arterial blood at least, others have reported similar acute effects following administration of hypertonic saline [20-23] and hypertonic saline/dextran [12] to hypovolemic animals.

Apparently, only Velasco et al. [20] and Lopes et al. [22] have offered explanations for these acute effects. In both instances, the authors attributed the increase in arterial PCO_2 and decrease in pH (seen after hypertonic saline administration to anesthetized, hypovolemic dogs) to ventilatory suppression. They [20,22] stated that ventilatory rate was decreased but did not provide any supporting data on either rate or minute volume. Results from our experiments suggest that ventilatory suppression is not the causative factor, at least not in conscious pigs; both expired and alveolar ventilation remained elevated during the acute stage of resuscitation [1]. A more plausible explanation is that hypertonic saline/dextran administration acutely causes a transfer of mixed-venous blood to the arterial circulation. Consistent with this interpretation are the directionally opposite changes in arterial and mixed venous PCO_2 (Fig. 2A,B), a near equivalency of arterial and mixed-venous pH (Fig. 2C,D), and the rapid increase in cardiac output with a resultant decrease in ventilation-perfusion ratio (V_A/Q_T) reported elsewhere [1]. Hypertonic saline, furthermore, causes vasodilation of the pulmonary vascular bed [24]. This interpretation necessarily implies that blood transit time in the pulmonary capillaries is too short to allow adequate diffusion of the elevated mixed-venous CO_2 load to the alveoli. However, if diffusion were a limiting factor, one might expect to see a sharp rise in the shunt fraction of pulmonary blood flow (Q_S/Q_T) shortly after administration of hypertonic saline/dextran; it rises only slightly [1].

A similar line of reasoning could account for the acute increase in venous PO_2 .

namely a transfer of arterial blood to the venous side of the systemic circulation. Decreased tissue O_2 demand [1], however, could also be a contributing factor.

In addition to changes in blood gas status, resuscitation with hypertonic saline/dextran induces a rapid transfer of water from the extra- to the intravascular space [3,12,25,26,27]. This transfer not only leads to a further reduction of blood hemoglobin level [1], but it also causes a further reduction of plasma protein level (Fig. 3D). Together, these resuscitation-induced changes lower buffer base concentration by approximately 6 mEq/L, a value that adds to the pre-existing, hemorrhage-induced decrement of 14.5 mEq/L to produce a total buffer base loss of 20.5 mEq/L. The effects of hemoglobin and plasma protein changes on blood-buffering capacity are seldom recognized in shock literature; clearly, the effects as seen here can be substantial.

Subsequent to the foregoing acute effects of hypertonic saline/dextran, some blood gas and acid-base variables rapidly reverted to control levels while others recovered slowly or not at all. At one extreme, venous PCO_2 reverted to, and remained at, prehemorrhage levels immediately after resuscitation. At the other extreme, venous PO_2 and saturation remained low, while buffer base and protein anion concentrations increased only slightly over the 4 h recovery period. The gradual return of plasma bicarbonate toward control levels was particularly significant since it implied that resuscitation with hypertonic saline/dextran effectively restored normal renal function, at least in terms of replenishing body bicarbonate stores. In this respect, Maningas [28] showed that hypertonic saline/dextran administration caused a rapid increase in the renal blood flow of hypovolemic pigs.

For the most part, these chronic effects were associated with a gradual reversion of hemorrhage-induced changes in metabolic and cardiopulmonary dysfunctions toward control levels. Resolution of the disparity between O_2 delivery and O_2 demand by hypertonic saline/dextran was a key factor underlying these resuscitation effects [1]. Resolution of blood gas and acid-base changes, therefore, was a secondary response to the metabolic actions of hypertonic saline/dextran.

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The studies described in this report were reviewed and approved by the Institutional Review Committee/Animal Care and Use Committee at Letterman Army Institute of Research. The manuscript was peer reviewed for compliance prior to submission for publication. In conducting the research described here the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," DHEW Publication (NIH) 85-23.



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